# ANALYSIS OF THE EFFECTIVENESS OF INDIVIDUALIZED TREATMENT REGIMENS FOR NONTUBERCULOUS MYCOBACTERIOSES

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**Introduction.** Nontuberculous mycobacteria (NTMB) are widespread microorganisms which are capable of affecting both people with immunosuppression and healthy people. They have a wide range of virulence. For the first time these pathogens were identified in 1885. In 1950 information that NTMB can cause pathological changes in the human body appeared. The genus *Mycobacterium* includes more than 150 species and 2 obligate pathogens (*M. tuberculosis and M. leprae*). Nontuberculous mycobacteria a lot of similar properties with pathogenic species and can cause pulmonary and extrapulmonary granulomatous lesions. Most patients who are infected with NTMB have background pulmonary diseases and / or immune system disorders. Often they are found on the background of chronic obstructive pulmonary disease (COPD), bronchiectasis, pneumoconiosis and have tuberculosis-like clinical signs. The incidence of nontuberculous mycobacterioses is growing rapidly worldwide, that's why they can become a serious problem for the health system soon [2-4]. This trend is especially noticeable in economically and socially developed countries, which have significantly reduced the burden of tuberculosis. Prevention of nontuberculous mycobacterioses is not developed that also significantly worsens the epidemic situation.

In addition, there are factors that contribute to detection of nontuberculous mycobacterioses:

- increasing the number of studied clinical samples
- improvement of laboratory methods detection and identification of NTMB
- recognition of NTMB as pathogens

NTMB can be divided into groups according to the speed and character of growth. According to the speed of growth NTMB can be classified as following:

- Slow-growing NTMB are growing for more than 14 days and include *M. avium complex (M. avium and M. intracellulare), M. kansasii, M. xenopi, M. simiae, M. szulgai, M. scrofulaceum, M. malmoense, M. terrae-nonchromogenicum complex, M. haemophilum*, and *M. genavense*. The optimal temperature for their growing is (except *M. haemophilum* which growth at 28-30$^0$C and *M. xenopi* which growth at 42$^0$C). Later other species of NTMB were isolated: *M. celatum, M. interjectum, M. confluentis, M. triplex, M. lentiflavum, M. branderi, M. conspicuum, M. cookii, M. asiaticum*.
- NTMB with intermediate growth speed are growing for 7-10 days and include *M. marinum* and *M. gordonae*. Their colonies are usually pigmented. The optimal temperature for *M. marinum* growth is 30$^0$C, for *M. gordonae* it is 35$^0$C.
- Rapid-growing NTMB grow up to 7 days. *M. fortuitum* complex is the most widespread among them. It forms uncolored colonies. Also this group include M. chelonae subspecies, *M. abscessus, M. mucogenicum, M. smegmatis*

Classification of NTMB based on character of colonies:

- Non-chromogenic NTMB – cannot produce yellow pigment
- Photochromogenic NTMB – produce NTMB under the light
- Scotochromogenic NTMB – produce yellow pigment without light

Although the species composition of NTMB depends on geographic location, *M. avium* complex (MAC) prevails everywhere, *M. abscessus* takes the second place, *M. kansasii* takes the third place [5].

First, tuberculosis and mycobacterioses were treated by the standard scheme of TB chemotherapy because of the similarity of their clinical picture, but later it was found that some NTMB have primary resistance to antituberculosis drugs. In addition, it was found that mycobacterioses require longer treatment (12 months after sputum conversion). Mycobacterioses treatment regimens depend on the form of the disease (pulmonary, disseminated, lesions of the skin and soft tissues, lesions of lymph nodes), the type of NTMB and its resistance. Drug susceptibility test for NTMB also remains difficult because some species (eg, MAC, *M. kansasii*, some rapid-growing NTMB) show different sensitivities to drugs *in vitro* and *in vivo*. Currently it's recommended to add fluoroquinolones to treatment regimens, because they demonstrate a better effectiveness in vivo than *in vitro*. According to the data obtained by T.F. Otten, levofloxacin (500 mg/day) is the most effective drug in the treatment of nontuberculous mycobacterioses. Treatment of nontuberculous mycobacterioses has limited therapeutic choices, is long and expensive and often is associated with several complications and interruption of treatment as a result. On the other hand the problem is amplified by the fact that existing recommendations for management of patients with mycobacteriosis are based primarily on expert opinion because of the lack of statistical data [6-9].

In the treatment of mycobacteriosis caused by *M. avium* complex clarithromycin was effective in combination with rifampicin and ethambutol, moxifloxacin in combination with clarithromycin was effective against *M. kansasii* [10].

Another important question still is criteria for differentiation of mycobacteriosis as a disease from finding NTMB as saprophytes, and thus - the need for treatment. Therefore, the decision to start treatment is a complex and individualized process when all "pluses" and "minuses" must be weighed.

Despite the fact that in Ukraine as well as worldwide there is growing incidence of nontuberculous mycobacterioses, there are still no standardized protocols of diagnosis and treatment of mycobacterioses in our country, which makes impossible prescribing of adequate chemotherapy and worsens the prognosis.

**Aim.** To analyze the effectiveness of chemotherapy regimens for patients with nontuberculous mycobacteriosis

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who were registered in Kharkiv region and its dependence on the character of growth of NTMB.

**Materials and methods.**

We have retrospectively studied medical histories of 26 patients (5 women and 21 men of average age - 38 ± 15 years) in whom tuberculosis wos diagnosed by the results of X-ray and sputum microscopy during 2014-2016. To confirm the diagnosis, patients were examined by diagnostic algorithm, approved by Order №620 of Ukrainian Ministry of Health from 09.04.2014, which included chest X-ray, double microscopic examination of sputum, sputum culture in system BACTEC and on Lowenstein-Jensen media, molecular-genetic test (GeneXpert MTB / RIF) and routine laboratory tests. Nontuberculous mycobacteriosis was diagnosed basing on growth of NTMB in system BACTEC and then it was verified by the following criteria:

- Microscopy: absence of Cord-factor formation (NTMB are located "loose" in smear)
- Negative immunochromatographic test (ID-test)
- Negative GeneXpert MTB/RIF

Then obtained NTMB were identified for likely pathogens on the basis of Runyon classification and modified classification, approved by Ukrainian Ministry of Health No 45 from 06.02.2002, in which the NTMB growth rate, nature and color of the colonies were taken into account.

As a result of research it was determined that 17 patients had chromogenic NTMB with slow growth and 9 patients - non-chromogenic NTMB with slow growth (Table. 1)

**Table 1 –Distribution of pathogens**

| Group of mycobacteria | Number |
|---|---|
| Slow-growing chromogenic NTMB (*M. kansasii, M.gordonae, M. marinum)* | 17 (65,4%) |
| Slow-growing non-chromogenic NTMB *(M. avium, M. intracellulare, M.xenopi)* | 9 (34,6%) |

Standard regimens of antituberculosis chemotherapy were prescribed to all the patients:

- 2HRZE – standard scheme for treatment of susceptible TB – 16 patients
- 2R(Rfb)Z(E)LfxKm – individual scheme – 6 patients
- 2R(Rfb)Z(E)LfxClr – individual scheme – 2 patients

where R – Rifampicin, Rfb – Rifabutin, де R – рифампіцин, Rfb – рифабутін, Z – Pyrazinamide, E – Ethambutol, Lfx – Levofloxacin, Clr – Clarithromycin, Km – Kanamycin. These schemes predicted daily administration of drugs, the analysis was carried out in 2 months. Apparently, this schemes differed from those proposed by CDC (Table. 2) [11-13].

**Table 2 – Schemes proposed by CDC for treatment of nontuberculous mycobacterioses**

| NTMB | Treatment |
|---|---|
| *M. avium complex* | Clarithromycin or azithromycin<br>+ ethambutol<br>+ rifampicin |
| *M. abscessus* | 1 macrolide<br>+ 1 parenteral drug (amikacin, cefoxitin, imipenem) |
| *M. kansasii* | Isoniazid<br>+ ethambutol<br>+ rifampicin |
| *M. marinum* | Clarithromycin or azithromycin or doxycycline, or trimethoprim-sulfamethoxazole<br>+ ethambutol<br>+ rifampicin |
| *M. xenopi* | Clarithromycin<br>+ ethambutol<br>+ rifampicin<br>± fluoroquinolone |
| *M. fortuitum* | 2 drugs, which set the sensitivity NTMB from the following list:<br>• tobramycin<br>• cefoxitin<br>• meropenem<br>• levofloxacin |

At the end of two months of treatment we have evaluated laboratory parameters of recovery (sputum conversion) and positive clinical and radiologic dynamics (disappearance or reduction in severity of intoxicational

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and local complaints, healing of cavities, resorption and consolidation of infiltrates).

According to the experts' opinion, the absence of acid-fast bacilli in sputum smear is the most important indicator of treatment effectiveness because clinical and radiographic dynamics is relatively slow.

**Results and discussion.**

Standard chemotherapy of tuberculosis by category 1 (2 HRZE) was prescribed the most often in patients with

In patients with slow-growing non-chromogenic NTMB all the 3 schemes were effective. We obtained expressed positive clinical and radiographic dynamics, disappearance of intoxication, sputum conversion, chromogenic slow-growing NTMB (70.6%). This scheme was not too effective, because at the sputum conversion was observed only in 83.3% of patients to the end of the second month of treatment, positive clinical and radiological dynamics occurred only in 41.7% of patients. However, in patients receiving individual scheme (2R (Rfb) Z (E) LfxKm) we observed fast positive clinical and radiological dynamics and sputum conversion by the end of the second month. Substitution of kanamycin with clarithromycin in 1 patient did not give a positive effect. significant resorption and consolidation of foci in lung tissue, healing of cavities.

It should be noted that 2 patients (1 in each group) have abandoned the treatment but follow-up they we have recorded self-recovery in them.

**Table 3 – Results of patients' treatment**

| Treatment regimens | Slow-growing chromogenic NTMB | Slow-growing non-chromogenic NTMB |
|---|---|---|
| 2HRZE/4HR | 12 (70,6%) | 4 (44,44%) |
| Laboratory recovery | 10 (83,3%) | 4 (100,0%) |
| Clinical and radiological recovery | 5 (41,7%) | 3 (75,0%) |
| 2R(Rfb)Z(E)LfxKm /10RELfx | 3 (17,6%) | 3 (33,3%) |
| Laboratory recovery | 3 (100,0%) | 3 (100,0%) |
| Clinical and radiological recovery | 3 (100,0%) | 2 (66,7%) |
| 2R(Rfb)Z(E)LfxClr/ 10RlfxClr | 1 (5,9%) | 1 (11,1%) |
| Laboratory recovery | 0 | 1 (100%) |
| Clinical and radiological recovery | 0 | 1 (100%) |
| Self-healing | 1 (5,9%) | 1 (11,1%) |

**Conclusions.** Thus we have seen a significant prevalence of chromogenic slow-growing NTMB among isolated mycobacteria. Individual treatment regimens with the addition of fluoroquinolones and aminoglycosides were effective for them. All the 3 treatment regimens were effective in patients with non-chromogenic slow-growing NTMB which allows us to use in them standard chemotherapy regimen with first-line anti-TB drugs, which in turn will save in this category of patients time and money.

The problem of mycobacterioses is not still well understood by pulmonologists. Until now, many patients with nontuberculous mycobacterioses obtain treatment with a diagnosis of "tuberculosis" or are observed over a number of chronic lung diseases. Situation is also complicated with clinical and radiological similarities of mycobacterioses and tuberculosis. And in addition timely detection of NTMB is complicated with widespread belief that mycobacterioses affect only people with immunosuppression.

International experts say that we have to develop and implement reliable methods to identify the species NTMB for successful treatment because treatment regimen should be individualized and based on NTMB sensitivity to drugs. It is also necessary to put into practice strict criteria and algorithms to choose treatment regimen and select patients for surgical treatment [14].

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Despite the fact that in Ukraine, as well as worldwide the incidence of nontuberculous mycobacterioses is growing, in our country there are still no standardized protocols for their diagnosis and treatment, which makes it impossible to prescribe adequate chemotherapy and worsens the prognosis of treatment. We have retrospectively studied medical histories of 26 patients who were diagnosed with "pulmonary non-tuberculous mycobacteriosis" during 2014-2016. The diagnosis of "non-tuberculous mycobacteriosis" was established based on the growth of non-tuberculous mycobacteria (NTMB) in BACTEC system, and then verified by the absence of Cord-factor formation, negative immunochromatographic test, negative GeneXpert MTB / RIF. Based on the results of the studies, it was determined that 17 patients had slow-growing chromogenic NTMB and 9 patients had slow-growing non-chromogenic NTMB. With the use of 2HRZE regimen, 83.3% of patients with slow-growing chromogenic NTMB underwent laboratory recovery, and only 41.7% of patients had clinical and X-ray recovery. However, patients who received the individual regimen (2R(Rfb)Z(E)LfxKm) had a rapid positive dynamics, clinical, radiological and laboratory recovery until the end of intensive phase. In patients with slow-growing non-chromogenic NTMB, all three regimens (2HRZE, 2R(Rfb)Z(E)LfxKm, 2R(Rfb)Z(E)LfxClr) proved to be effective. We believe that it is necessary to improve level of identification of NTMB for the timely appointment of an adequate chemotherapy regimen.

**Keywords**. Nontuberculosis mycobacterium, chemotherapy,

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